## REMARKS

The present remarks are responsive to the Office Action mailed on November 2, 2009. Claims **44-61**, **63-68**, **71**, and **73-74** are pending in this application. Claims **1-43**, **62**, **69**, **70**, and **72** were canceled by previous amendment. Also accompanying this communication is a petition to extend the prosecution on this matter for three months and the appropriate fee.

By the following remarks, pending claims **44-61**, **63-68**, **71**, and **73-74** are believed to be in condition for allowance and are again presented for reconsideration.

### Discussion of the Office Action

In the Office Action of November 2, 2009, the Examiner rejected claims **44-61**, **63-68**, **71**, and **73-74** under 35 U.S.C. §112, first and second paragraphs, he rejected claims **44**, **47-50**, **52**, **53**, **55**, **61**, **63-68**, and **71** under 35 U.S.C. §102(b) as being anticipated by Toro et al. (journal of Chromatography A, 2000) and he rejected claims **45**, **46**, **51**, **54**, **56-60**, **73**, and **74** under 35 U.S.C. §103(a) as being unpatentable over Toro in view of Aebersold et al. (Chemical Review, 2001).

### Discussion of the rejections of claims 44-61, 63-68, 71, and 73-74 under 35 U.S.C. §112, first paragraph

Claims **44-61**, **63-68**, **71**, and **73-74** stand rejected under 35 U.S.C. §112, first paragraph, because the Examiner states that the specification, "while being enabling for [sic] reference sample that has substantially the same peptide profile as the first peptide mixture, does not reasonably provide enablement for [sic] reference sample that has any peptide profile." The Examiner goes on to state that "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to use the invention commensurate in scope with these claims. The calculation of the normalization factor is based on the assumption that the reference sample has substantially [sic] same

peptide profile as the first peptide mixture (see specification page 23, lines 13-14)." based on these states, the Examiner then concludes that "[i]t would have been an undue experimentation for a routineer in the art to search for a method to calculate [sic] normalization factor with any reference sample, as recited in claims 44, 63, 71, 73 and 74." The Application must respectfully traverse the rejection in light of the following comments.

Regarding independent pending claims **44, 63, 71, 73,** and **74**:

The Court of Appeals for the Federal Circuit stated in National Recovery Techs, Inc. v. Magnetic Separation Syst., Inc, 49 USPQ 2d 1671, 1675-76 (Fed. Cir. 1999),

> *"the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."*

And in Fiers v. Revel 25 USPQ 2d 1601, 1607 (Fed. Cir. 1993), the CAFC also stated:

> "[A] *specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken in as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statement contained therein which must be relied on for enabling support."*

Furthermore, in Staeehelin v. Secher, 24 USPQ 2d 1513, 1516 (B.P.A.I. 1992), the Board of Appeals stated,

> *"... the* ***law does not require*** *a specification to be* ***a blueprint*** *in order to satisfy the requirement for enablement under 35 USC 112, first paragraph."*(emphasis added)

Applicant respectfully submits that the basic requirements to practice the invention without undue experimentation is found within the application and is thus

reasonable without doubt to those of skilled in to provide enablement, as mandated under National Recovery Techs, Inc., Fiers, and Staeehelin. In particular, so as to comport with the above cited cases, Applicant respectfully notes that the standard for enablement is not whether a feature has explicit antecedent support in the specification. Rather, MPEP § 2164.01 states in part, that "[a]ny analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as **to enable one skilled in the pertinent art** to make and use the claimed invention" (emphasis added). In other words, the Examiner should ask "is the experimentation needed to practice the invention "undue or unreasonable" by such a person. The factors for making a determination of undue experimentation are rigorous and include, but are not limited to (See MPEP § 2164.01(a)):

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Applicant respectfully notes that these factors **have not been considered on the record** and calls upon the Examiner to provide his detailed analysis.

In the instant case, so as to provide clarification, the processes discussed herein utilize three steps and respective terms: 1) calculating abundances of mass-

analyzed peptide using a reconstructed ion chromatogram of these peptides; 2) normalizing the calculated abundances of the one or more mass analyzed peptides of the first peptide mixture and 3) calculating a relative quantity for the one or more mass analyzed peptides of the first peptide mixture versus the same peptide in the reference peptide mixture.

Applicant respectfully submits that a person of ordinary skill in the art readily appreciates that normalization is important to take into account differences in total concentration (injected amount) of a reference sample and a first sample as described in the present invention and could utilize one of the many example procedures of normalization of the present invention without undue experimentation if called upon (see page 12, lines 15-31).

To illustrate, if, for some reason, the total concentration (injected amount) of the first sample was, for example, two-fold higher than the reference sample, the calculated abundances of a mass-analyzed peptide in this sample will be two-fold higher than in the reference sample. One skilled in the art would recognize that for the purposes of the quantitative proteomic analysis they are actually the same. To take into account the variations in the total concentration (injected amount) and variations in the instrument performance between the reference sample and the first sample, one skilled in the art in reading the specification of the present invention would apply a desired normalization procedure so as to calculate a normalization factor. An example normalization method that could be reasonably applied when read by one skilled in the art, i.e., a "routineer," is presented on page 12, lines 23-24 of the specification of which teaches a normalizing of each peptide (protein) to ALL IDENTIFIED PEPTIDES (PROTEINS) in the mixture. Such an example step is not based on assumptions that the reference sample has substantially the same peptide profile as the first peptide mixture, as asserted by the Examiner. After this step, the calculated abundance can be converted to normalized calculated abundances as also described in the passages that follow (lines 24-33 on page 12, bridging page 13, line 1-9). Added together, the normalized calculated

abundances of all proteins in the mixture should give 100%. Such a common normalization step is also performed on the reference sample. Please take note that although the term "relative "abundance could have been used here instead of normalized, the term "relative" was instead saved as limitations in the last elements for each of independent claims **44**, **63**, **71**, **73**, and **74** to provide the comparison of the first mixture and reference mixture. In particular, calculating a relative quantity refers to the ratio (normalized calculated abundance of a peptide in the first mixture)/ (normalized calculated abundance of a peptide in the reference mixture). To conclude, there are examples of normalization in the present invention, as discussed above, that are reasonably described to provide enablement to those skilled in the art to appreciate the operations. It necessarily follows that it would not have been "undue experimentation for a routineer in the art to search for a method to calculate a normalization factor with any reference sample..."

This last principle is also exemplified in Cedarapids, Inc. v. Nordberg, Inc Civ. App. 95-1529, slip op. 5-6 (Fed. Cir. Aug. 11, 1997) as follows,

> *"While it may require experimentation to arrive at the optimum level of the simultaneous increases for various size crushers, we have never held that a patent must disclose information sufficient to manufacture a commercial product incorporating the invention."*

Accordingly, it is respectfully submitted that the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. Thus, the Applicant also respectfully submits that the 35 U.S.C. 112, first paragraph rejection of claims **44-61**, **63-68**, **71**, and **73-74** is improper and is requested to be withdrawn.

Discussion of the rejections of claims 44-61, 63-68, 71, and 73-74 under 35 U.S.C. §112, second paragraph

Claims **44-61**, **63-68**, **71**, and **73-74** stand rejected under 35 U.S.C. §112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. The Examiner cites MPEP §2172.01 and states that the "omitted steps are: calculating [sic] normalization factor by excluding all ratios (peptides of analyte to reference) not within the median (0.92) +/- the standard devition (0.42)." The Examiner goes on to state that "[a]s disclosed in the specification, this step is **essential** for the step of comparing the calculated abundance of mass analyzed peptides of the first peptide mixture with an abundance of peptides in a peptide mixture of [sic] reference sample...." (underlining and bolding for emphasis). Applicant respectfully traverses the rejection and respectfully submits that this statement is contrary to, and inconsistent with, both Mayhew and the MPEP.

MPEP §2172.01 states that "[a] claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record may be rejected under 35 U.S.C. 112, **first paragraph**, as not enabling. *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976)" (emphasis added).

MPEP §2164.08(c) which mirrors MPEP §2172.01, states that "[a] feature which is which is **taught as critical** in a specification and is not recited in the claims should result in a rejection of such claims under the enablement provision section of 35 U.S.C. 112. See *In re Mayhew*, 527 F.2d 1229, 1233, 188 USPQ 356, 358 (CCPA 1976)" (emphasis added). In determining whether an unclaimed feature is critical, **the entire disclosure must be considered**. **Features which are merely preferred are not to be considered critical**. *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976) (emphasis added).

The Applicant submits that the Examiner in his rejection mailed November 2, 2009, asserts in error that the above cited calculated normalization factor (i.e., a calculated factor by excluding all ratios not within the median (0.92) +/- the standard devition (0.42)) is **essential** under the provisions of MPEP §2172.01. Respectfully, the Applicant submits that the Examiner bases his assertion upon a provided example of the present invention (i.e., Example 2, starting on page 21) that is merely utilized to demonstrate a utility of the present invention but not an essentiality. This assertion is made by the Examiner without any wording expressly or impliedly in the application that states the calculated normalization factor by excluding all ratios not within the median (0.92) +/- the standard deviation (0.42) is necessary or essential. In fact and in contrast, the Applicant expressly teaches (see page 12, lines 31-33 bridging page 13, lines 1-3) that "[p]roteins that are present in different amounts in the different experiments (e.g. the proteins for which relative quantitation information is desired) **can be excluded** by calculating the standard deviation (e.g., the median standard deviation) of peak area ratios, excluding all proteins for which the ratio is are [sic] not within the median standard deviation, and recalculating the average (e.g., median) of the ratios for the remaining proteins" (emphasis added).

The Applicant calls upon the Examiner to note the use of the passive tense "**can**" as highlighted in the above cited section. This use of the passive tense is contrary to any language of "must" or "it is critical that" or it is "essential" and in fact there is no wording of "essentiality" found in the cited section provided by the Examiner, or anywhere else within the four corners of the application to even remotely suggest that a calculated normalization factor having specific limiting parameters, i.e., excluding all ratios not within the median (0.92) +/- the standard deviation (0.42), is necessarily required so as to trigger the provisions found in MPEP §2164.08(c) and/or MPEP §2172.01. Moreover, the Applicant would also like to draw the Examiner's attention to the sentence immediately preceding the cited section by the Examiner (i.e., lines 9-11, page 23), wherein the Applicant in his teaching of Example 2, states that "[t]he ratios of

the peak areas were normalized against an **experiment-dependent correction factor**" (emphasis added). Such a wording connotes that the correction factor can change based on the experimental conditions so as to comport with the other teachings of the present invention. Please also note on page 13, line 7, wherein the Applicant also states, "[o]ther known methods for normalizing the peak areas can also be used." Thus, if the entire disclosure is considered, as mandated under MPEP §2164.08(c) and *In re Goffe*, it is evident that the present application does not necessarily require the calculated normalization factor step as asserted by the Examiner. It is but an example of a way but not an essential way to enhance the data of the present invention.

Accordingly, Applicant respectfully submits that the 35 U.S.C. §112 rejection of claims **44-61, 63-68, 71**, and **73-74** is improper and respectfully requests that the rejection be withdrawn.

Rejection of claims 44, 47-50, 52, 53, 55, 61, 63-68, and 71 under 35 U.S.C. §102(b)

As set forth above, claims **44, 47-50, 52, 53, 55, 61, 63-68**, and **71** stand rejected under 35 U.S.C. §102(b) as being anticipated by Toro et al. (journal of Chromatography A, 2000). Regarding each of independent claims **44, 63**, and **71**, the Examiner as part of the rejection, states that with respect to the last element of each respective independent claim that Toro teaches: "calculating a relative quantity...by **comparing** the calculated abundance of mass analyzed peptides of **the first peptide** mixture **with an abundance of peptides in a reference sample** (see page 104, Table 6),...." (emphasis added). The Applicant must traverse the rejection in light of the comments contained hereinafter.

> Under §MPEP 2129, "To anticipate a claim, the reference must teach every element of the claim"

In addition,

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. V. Union Oil Co. of California, 814n F. 2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Moreover, the Federal Circuit has stated:

> "For a prior art reference to anticipate a claim, the reference must disclose each and every element of the claim with sufficient clarity to prove its existence in the prior art." In re Spada, 911 F.2d 705, 708, 15 USPQ 2d 1655, 1657 (Fed. Cir. 1990).

The last element of claim **44** for the present invention states:

> "calculating a relative quantity for the one or more mass analyzed peptides of the first peptide mixture by **comparing the calculated abundance of the one or more mass analyzed peptides of the first peptide mixture with an abundance of one or more peptides in a reference sample**, wherein the reference sample is external to the first peptide mixture and wherein the reference sample and the first peptide mixture are unlabeled." (emphasis added)

The last element of claim **63** for the present invention states:

> "means for calculating a relative quantity for the one or more mass analyzed peptides of the first peptide mixture by **comparing the calculated abundance of the one or more mass analyzed peptides of the first peptide mixture with an abundance of one or more peptides in a reference sample** which is external to the first peptide mixture, wherein

the reference sample and the first peptide mixture are unlabeled." (emphasis added)

The last element of claim **71** for the present invention states:

"calculate a relative quantity for the one or more mass analyzed peptides of the first peptide mixture by **comparing the calculated abundance of the one or more mass analyzed peptides of the first peptide mixture with an abundance of one or more peptides in a reference sample**, the reference sample being external to the first peptide mixture and wherein the reference sample and the first peptide mixture are unlabeled." (emphasis added)

Regarding independent claims **44**, **63**, and **71**, Applicant respectfully submits that Toro does not disclose nor suggest Applicant's claimed limitations of comparing the calculated abundance of the one or more mass analyzed peptides of the first peptide mixture with an abundance of one or more peptides in a reference sample, as also shown boded above in each of the last element of the respective claims. The Examiner in the rejection mailed 11/02/2009, specifically points to page 104, Table 6 as the cited section in Toro so as to assert his position that Toro describes the aforementioned limitations. Respectfully, the Applicant submits that the cited section by the Examiner in Toro does not teach "comparing the calculated abundance of the one or more mass analyzed peptides of the first peptide mixture with an abundance of one or more peptides in a reference sample," as claimed and described in the present invention **but instead teaches** a method of quantitation by providing a mixture of peptides and then calculates quantity by the aid of a predetermined calibration curve(s) resultant from diluted sets of the same peptides. Specifically, Toro teaches at the end of page 103 which bridges page 104 that "[t]he quantitation was performed by external calibration, plotting peak area versus concentration injected into the system using positive ion mode and SIM of the $[M + nH]^{n+}$

ions." Such a method is not the same as comparing a first mixture with a reference sample mixture as provided in the specification of the present invention. Thus, Toro and the present invention are clearly separate and distinct processes.

Accordingly, Applicant respectfully submits that because Toro does not teach every element of the invention, as mandated under §MPEP 2129, Verdegaal Bros., and In re Spada, the rejection under 35 U.S.C. §102(b) of independent claims **44, 63**, and **71** and dependent claims **47-50, 52, 53, 55, 61, 64-68**, which directly or indirectly depend from respective independent claims **44** or **63**, and thus also inherit all of their limitations, is improper and should be removed.

Rejection of claims 45, 46, 51, 54, 56-60, 73 and 74 under 35 U.S.C. §103(a)

As set forth above, claims **45, 46, 51, 54, 56-60, 73** and **74** stand rejected under 35 U.S.C. §103(a) as being unpatentable over Toro in view of Aebersold et al. The Applicant must traverse the rejection.

Regarding claims **45, 46, 51, 54, 56-60**, such claims depend either directly or indirectly from independent base claim **44** and thus inherit each and every limitation of the base claim. As discussed above with respect to the rejection under 35 U.S.C. §102(b) of base claim **44**, Toro does not teach nor does he suggest the limitation of "**comparing the calculated abundance of the one or more mass analyzed peptides of the first peptide mixture with an abundance of one or more peptides in a reference sample**." In addition, the Applicant respectfully submits that Toro even in combination with Abersold also does not teach or suggest the above bolded limitation so as to warrant an obviousness rejection of independent claim **44**.

Under MPEP §2143.01,

> "If an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious." In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Accordingly, Applicant respectfully submits that the rejection under 35 U.S.C. §103(a) of claims **45, 46, 51, 54, 56-60** is improper and is requested to be removed, as mandated under MPEP §2143.01.

Regarding independent claims **73** and **74**, the Examiner had stated that the process and apparatus recited in the instant claims can be derived from Toro's teaching by simply substituting peptide with the compound. This statement is in error. First, the last element of claim **74** also has the similar limitations found in the last element of claim **73**, i.e., "**comparing the calculated abundance** of the one or more mass analyzed compounds **of the biological sample** with **an abundance of one or more compounds in a reference sample**." Again, Toro calculates his quantity by the aid of a predetermined calibration curve and not by comparison with a reference sample. This is in contradistinction to the limitations found in either of the last elements of claims **73** and **74** of the present invention as discussed in detail above. Therefore, it is beyond reason to assert that the processes and apparatus recited in the instant claims can be derived from Toro's teaching by simply substituting peptide with compound.

Accordingly, Applicant also respectfully submits that the rejection of claims **73** and **74** under 35 U.S.C. §103(a) is also improper and is requested to be removed.

## CONCLUSION

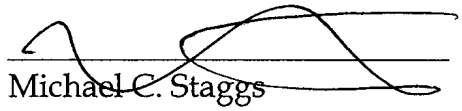
The undersigned respectfully submits that, in view of Applicant's amendments and comments, the rejections of the claims raised in the Final Office Action dated November 2, 2009 have been fully addressed and overcome, and the present application is believed to be in condition for allowance.

It is respectfully requested that this application be reconsidered, that remaining pending claims **44-61**, **63-68**, and **71**, **73-74** be allowed and that this case be passed to issue. In the event that the Examiner finds any remaining impediment to the prompt allowance of these claims that can be clarified with a telephone conference, he is respectfully requested to initiate the same with the undersigned at (408) 965-6200.

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this communication to Deposit Account No. 50-3267.

Dated: April 12, 2010

Respectfully submitted,

By: 

Michael C. Staggs
Reg. No. 50,938

Thermo Fisher Scientific Inc.
ATTN: IP Department
355 River Oaks Parkway
San Jose, California 95134
Tel: (408) 965-6200
Fax: (408) 965-6010